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Topological Modeling of Maximum Acceptor Superdelocalizability A_{max} Vis a Vis Toxicity of Some Aromatic Aldehydes.

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Abstract

The quantitative Structure-Toxicity Relationships (QSTR) was performed for a set of 77 aromatic aldehydes using Maximum Acceptor Superdelocalizability **A_{max}** and topological indices. Multiple regression analysis (MLR) was used for obtaining statistically significant models. . The maximum acceptor superdelocalizability (A_{max}) accounts for the interaction with the biomacromolecules into the cells. This, therefore, is one of the important parameter for the exhibition of toxicity of the aldehydes used. However, use of A_{max} alone not successful for modeling the toxicity. We have, therefore used topological indices along $A_{max.}$ For doing so, we have to modeled A_{max} using topological indices.The results show that statistically significant models are obtained in multi-parametric regression model. The Randic connectivity and Kier and Hall type indices are useful in modeling of **A_{max}**.

Keywords: Toxicity, Maximum Acceptor Superdelocalizability aromatic aldehydes, topological indices, QSTR, regression analysis,

Introduction

It has been known[1] that the information about the toxicity of industrial organic chemical to aquatic species can be obtained using molecular descriptors. This is due to fact that such a testing is carried out experimentally testing provides the most reliable data about the effect of chemicals. However, is time and resource demanding and not deemed suitable for screening of large numbers of potential toxicants. Prediction of toxicity based on QSARs has been thought of as an alternative approach[2].

Aldehydes are important intermediates in production of a variety of industrial processes, such as agrichemicals and pharmaceuticals. In particular, aldehydes are important in the flavor and fragrance industry[3]. Because of their inherent reactivity aldehydes are able to interact with the electron-rich biological macromolecules, in particular protein and nucleic acids and therefore have the potential to cause a number of adverse effects[4] Excess toxicity of aldehydes to fish is thought to be through specific, irreversible, electrophilic mechanisms[5].

Fish acute toxicity studies conducted by McKim *et al*[6] demonstrated that the physiological responses observed in rainbow trout exposed to model aldehydes, including benzaldehyde, is membrane irritation brought on by a concentration response. As direct acting electrophiles aldehydes are also skin-sensitizers[7] and genotoxicants[8].

As mentioned in literature[4] the maximum acceptor superdelocalizability (A_{max}) accounts for the interaction with the bio-macromolecules into the cells. This, therefore, is one of the important parameter for the exhibition of toxicity of the aldehydes used. However, we have not used A_{max} as one of the correlating parameter for modeling the toxicity. Instead we have used topological indices for this purpose So, it becomes necessary for us to correlate A_{max} with topological indices. That is we have to model A_{max} using topological indices**.** In this studies we examine the relationship between topological indices and Maximum Acceptor Superdelocalizability Amax of aromatic aldehydes.

Dataset and methodology used

The values of A_{max} of 77 aromatic aldehydes were taken from the work of Schultzand Netzeva[4].Various topological indices were calculated

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by DRAGON software[11] .structure optimization was done by ACD lab software[12]

Model development

Molecular modeling was carried out by regression analysis in that the method of maximum R^2 was adopted .The regression analyses were done using Regress-1 provided by Prof. I. Lukovits , Hungarian Academy of Sciences, Budapest, Hungary and Data analysis program Microsoft 2003. Multiple linear regression analysis was employed in the modeling of A_{max} .

Results and Discussion

For the set of 77 aromatic aldehydes the values of **A_{max}** and various topological indices were calculated . Using various combinations of descriptors we obtained 15 statistically significant models. Such models are shown in Table 1. The statistically data and quality of correlation indicated that models containing 9 or more correlating parameters yielded equally good quality models for modeling $A_{max.}$ However ,all these models contained one or more correlating parameters in that the coefficient are much smaller than their respective standard error and are therefore, need not be considered.

A perusal of Table 1 indicates that 8- parametric model is the most appropriate model for modeling A_{max}. This model is found as below.

$$\mathrm{Amax} = 0.2150 + 0.0287(\pm 0.0037)Ms + 0.0020(\pm 0.0007)ZM_1 - 0.0308(\pm 0.0097)\chi^3 - 0.0348(\pm 0.0095)^2\chi^V + 0.1267(\pm 0.0184)^3\chi^V - 0.0823(\pm 0.0128)^4\chi^V + 0.0075(\pm 0.0039)I_2 - 0.0075(\pm 0.0034)I_5$$

$$N = 77, R^2 = 0.6457, Se = 0.0096, F = 15.491$$

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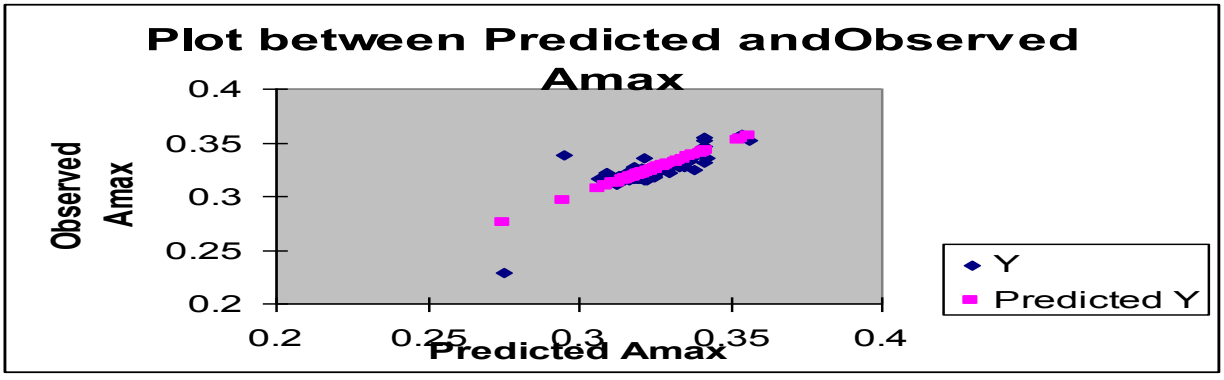
The above model shows that Amax is directly proportional to Ms,ZM_1, $^3\chi^V$ and I_2 it means that increase in the values of these parameters favor Amax. while decrease in the values of χ^3, $^2\chi^V$, $^4\chi^V$ and I_5 increase the value of Amax. Here I_2 and I_5 are dummy parameter stand for substitution at 3rd position and trisubstituted derivatives respectively.

This eq. **(1)** indicates that Amax is governed by connectivity indices. The eq (1) involves both Randic as well as Kier–Hall connectivity indices. Obviously, we can argue that connectivity is responsible for A_{max}. From the results discussed so for we conclude that use of Randic and Kier – Hall connectivity mimic A_{max} . It means that we need not have to use A_{max} as separate correlating parameter for modeling the toxicity of the aldehydes used. They are taken care of by the Randic and Kier–Hall connectivity indices them self.



The above graph indicates close resemblance between observed and predicted Amax by model equation 1.

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Table 1 Modeling of A_{max} for Aquatic Toxicity of 77 Aromatic Aldehydes using topological indices.

Model.No	Parameters	S.e.	R^2	Adjusted R^2	F
1	Ms	0.0130	0.2829	0.2733	29.588
2	Ms,I_5	0.0128	0.3160	0.2975	17.091
3	Ms, $^3\chi^V$, $^4\chi^V$,.	0.0112	0.4858	0.4646	22.986
4	Ms, $^3\chi^V$, $^4\chi^V$,I_5	0.0106	0.5406	0.5151	21.182
5	Ms, $^3\chi^V$, $^4\chi^V$,I_2,I_5	0.0104	0.5649	0.5343	18.437
6	Ms, 2χV, 3χV, 4χV, I2,I5	0.0101	0.5933	0.5584	17.018
7	Ms, $^2\chi^V$, $^3\chi^V$, $^4\chi^V$, I_2,I_5,I_8.	0.0101	0.6024	0.5621	14.934
8	Ms,ZM1, χ^3, $^2\chi^V$, $^3\chi^V$, $^4\chi^V$, I_2,I_5.	0.0096	0.6457	0.6040	15.491
9	Ms,ZM1,JhetP ,χ^3, $^2\chi^V$, $^3\chi^V$, $^4\chi^V$, I_2,I_5..	0.0096	0.6534	0.6069	14.037
10	Ms,ZM1,JhetP, χ^3, $^2\chi^V$, $^3\chi^V$, $^4\chi^V$, I_2,I_5.,I_8.	0.0095	0.6600	0.6085	12.813
11	Ms,ZM1,JhetP χ^3, $^5\chi^V$, $^3\chi^V$, $^4\chi^V$, I_2,I_5.,I_8..	0.0095	0.6652	0.6086	11.742
12	Ms,ZM1,JhetP,, χ^3, $^5\chi^V$, $^3\chi^V$, $^4\chi^V$, I_1,I_2,I_5.,I_8.	0.0095	0.6698	0.6078	10.817
13	Ms,ZM1,JhetP, χ^3, $^5\chi^V$, $^3\chi^V$, $^4\chi^V$, I_1,I_3,I_4,I_5.,I_8	0.0095	0.6774	0.6109	10.177
14	Ms,ZM1,JhetP, , χ^3, χ^4, $^5\chi^V$, $^3\chi^V$, $^4\chi^V$, I_1,I_3,I_4,I_5.,I_6	0.0095	0.6827	0.6110	9.528
15	Ms,ZM1,JhetP, , χ^3, χ^4, $^5\chi^V$, $^3\chi^V$, $^4\chi^V$, I_1,I_3,I_4,I_5.,I_6,I_7.	0.0096	0.6838	0.6061	8.795

Table - 2 Names of Aromatic Aldehydes and values of A_{max} and different Topological indices

S.NO	Name Of The Compound	Amax	Ms	ZM1	X3	X2V	X3V	X4V
1	4-Nitrobenzaldehyde	0.3332	3.3	50	3.412	1.966	1.24	0.675
2	1-Naphthaldehyde	0.3166	2.33	60	4.248	2.686	1.95	1.353
3	4-Biphenylcarboxaldehyde	0.3169	2.29	68	4.785	3.106	2.154	1.385
4	4-Bromobenzaldehyde	0.322	2.56	40	2.713	2.585	1.535	0.806
5	4-Cynobenzaldehyde	0.3257	2.88	44	3.121	1.852	1.176	0.636
6	Benzaldehyde	0.317	2.58	34	2.302	1.529	0.936	0.532
7	p-Tolualdehyde	0.3158	2.48	40	2.713	2.029	1.213	0.645
8	4-Fluorobenzaldehyde	0.3215	3.15	40	2.713	1.669	1.006	0.541
9	4-Chlorobenzaldehyde	0.3248	2.72	40	2.713	2.106	1.258	0.667
10	4-Ethylbenzaldehyde	0.3158	2.38	44	3.121	2.213	1.524	0.832
11	Terephthaldicarboxaldehyde	0.3237	2.93	44	3.121	1.902	1.209	0.653
12	4-Anisaldehyde	0.3153	2.58	44	3.121	1.891	1.252	0.682
13	4-Ethoxybenzaldehyde	0.3147	2.48	48	3.241	2.12	1.327	0.809
14	4-Acetamidobenzaldehyde	0.3272	2.79	54	3.348	2.421	1.367	0.848
15	2-Tolualdehyde	0.3158	2.48	40	2.813	1.974	1.315	0.719
16	3-Tolualdehyde	0.3163	2.48	40	2.622	2.032	1.178	0.743
17	2-Chlorobenzaldehyde	0.3279	2.72	40	2.813	2.047	1.376	0.751
18	3-Chlorobenzaldehyde	0.3215	2.72	40	2.622	2.109	1.22	0.779
19	2-Nitrobenzaldehyde	0.3326	3.33	50	3.349	1.934	1.26	0.753

20	3-Nitrobenzaldehyde	0.3317	3.33	50	3.344	1.97	1.217	0.712
21	Phenyl-1,3-dialdehyde	0.3236	2.93	44	3.046	1.906	1.183	0.706
22	2-Anisaldehyde	0.3158	2.58	44	3.115	1.86	1.266	0.764
23	3-Anisaldehyde	0.3173	2.58	44	3.046	1.894	1.23	0.715
24	3-Bromobenzaldehyde	0.3219	2.56	40	2.622	2.589	1.478	0.997
25	3-Fluorobenzaldehyde	0.3222	3.15	40	2.622	1.673	0.985	0.58
26	2,4-Dichlorobenzaldehyde	0.335	2.82	46	3.134	2.627	1.652	1.05
27	2,4-Dimethoxybenzaldehyde	0.3184	2.58	54	3.875	2.226	1.568	0.916
28	2,4,5-Trimethoxybenzaldehyde	0.317	2.58	64	4.642	2.567	1.863	1.145
29	4-(Dimethylamino)benzaldehyde	0.3104	2.39	50	3.412	2.604	1.546	0.851
30	4-Phenoxybenzaldehyde	0.3166	2.37	72	4.935	3.102	1.995	1.239
31	2-Bromobenzaldehyde	0.3245	2.56	40	2.813	2.494	1.754	0.949
32	2-Fluorobenzaldehyde	0.3239	3.15	40	2.813	1.639	1.032	0.571
35	4-Isopropylbenzaldehyde	0.3157	2.33	50	3.412	2.939	1.739	0.959
36	Pentafluorobenzaldehyde	0.357	4.54	64	5.139	2.101	1.362	0.725
37	2-Chloro-5-nitrobenzaldehyde	0.3568	3.34	56	3.87	2.488	1.662	0.897
38	2-Chloro-6-fluorobenzaldehyde	0.3365	3.21	46	3.252	2.16	1.447	0.831
39	3-Cyanobenzaldehyde	0.3254	2.88	44	3.046	1.855	1.152	0.682
40	2-Chloro-3-hydroxy-4methoxy	0.3271	2.94	56	4.273	2.515	1.853	1.019
41	6-Chloro-2-fluoro-3-methylbenzaldehyde	0.3307	3.07	52	3.853	2.617	1.767	0.977
42	3-Chloro-2-fluoro-5(trifluoromethyl)benzaldehyde	0.3524	4.07	70	4.634	2.884	1.786	1.086
43	2,3,5-TriChlorobenzaldehyde	0.3413	2.91	52	3.645	3.13	2.183	1.324
44	2-Fluorenecarboxalzaldehyde	0.3164	2.19	82	5.85	3.868	2.954	2.238
45	2-Methyl-1-Naphthaldehyde	0.3183	2.28	66	4.713	3.135	2.307	1.561
46	4-Methyl-1-Naphthaldehyde	0.316	2.28	66	4.728	3.135	2.303	1.576
47	Phenanthrene-9-carboxaldehyde	0.3175	2.21	86	6.128	3.85	2.927	2.181
48	5-Hydroxy-2-nitrobenzaldehyde	0.3362	3.5	56	3.684	2.118	1.335	0.803
49	3-Hydroxy-4-nitrobenzaldehyde	0.3459	3.5	56	3.778	2.123	1.332	0.768
50	3-Hydroxybenzaldehyde	0.3196	2.93	40	2.622	1.713	1.006	0.598
51	3-Hydroxy-4-methoxybenzaldehyde	0.3169	2.86	50	3.557	2.049	1.339	0.78
52	3,4-Dimethoxy-5-hydroxy	0.3198	2.82	60	4.251	2.393	1.618	1.033
53	2,3-Dihydroxybenzaldehyde	0.319	3.2	46	3.4	1.833	1.173	0.644
54	2,5-Dihydroxybenzaldehyde	0.3258	3.2	46	3.149	1.861	1.138	0.636
55	3,4-Dihydroxybenzaldehyde	0.3183	3.2	46	3.284	1.866	1.136	0.614
56	3,4,5-Trihydroxybenzaldehyde	0.3218	3.42	52	3.783	2.026	1.228	0.693
57	2,3,4-Trihydroxybenzaldehyde	0.3231	3.42	52	3.988	1.989	1.288	0.68
58	2,4,6-Trihydroxybenzaldehyde	0.3273	3.42	52	3.482	2.016	1.239	0.729
59	2,4-Dihydroxybenzaldehyde	0.3252	3.2	46	3.134	1.861	1.141	0.632
60	3-Ethoxy-2-hydroxycarboxaldehyde	0.317	2.75	54	3.821	2.245	1.457	0.906
61	3-Methoxysalicylaldehyde	0.3174	2.86	50	3.686	2.016	1.377	0.799
62	3,5-Dibromosalicylaldehyde	0.2281	2.83	52	3.645	3.713	2.247	1.934
63	4,6-Dimethoxy-2-hydroxybenzaldehyde	0.3237	2.82	60	4.251	2.38	1.667	0.993
64	2-Hydroxy-3-nitrocarboxaldehyde	0.3543	3.5	56	3.912	2.09	1.37	0.791
65	2-Chloro-4-hydroxy-carboxaldehyde	0.3348	3.01	46	3.134	2.231	1.438	0.831
66	4-Hydroxy-3-nitrobenzaldehyde	0.3521	3.5	56	3.8	2.123	1.332	0.76
67	4-Hydroxybenzaldehyde	0.3166	2.93	40	2.713	1.709	1.029	0.553
68	2-Hydroxy-1-naphthaldehyde	0.3244	2.59	66	4.713	2.837	2.066	1.408
69	5-Bromovanillin	0.3264	2.83	56	4.084	3.026	2.011	1.277
70	4-Hydroxy-1-naphthaldehyde	0.3191	2.59	66	4.728	2.837	2.062	1.409
71	5-Bromosalicylaldehyde	0.3212	2.88	46	3.149	2.737	1.61	0.999
72	5-Chlorosalicylaldehyde	0.3238	3.01	46	3.149	2.257	1.352	0.8
73	2-Hydroxybenzaldehyde	0.3177	2.93	40	2.813	1.677	1.064	0.587
74	3-Bromo-4-hydroxybenzaldehyde	0.3276	2.88	46	3.284	2.683	1.743	0.993
75	3-Methoxy-4-hydroxybenzaldehyde	0.3175	2.86	50	3.573	2.049	1.34	0.768
76	3,5-Dibromo-4-hydroxybenzaldehyde	0.3388	2.83	52	3.783	3.66	2.384	1.875
77	3-Ethoxy-4-hydroxybenzaldehyde	0.317	2.75	54	3.708	2.278	1.42	0.875

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